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## CLINICAL OBSERVATIONS ON INFLUENZA WITH SPECIAL REFERENCE TO THE BLOOD AND BLOOD PRESSURE \*

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This is a report of observations on influenza at the Michael Reese Hospital of Chicago during the epidemic of 1918. There were 546 cases of influenza admitted between September 20 and December 31, 185 males and 361 females. The ages varied from 3 months to 80 years, the greatest age incidence being between 20 and 30 years (chart 1). In 55 cases an exhaustive daily study was made of blood, urine, and blood pressure. In all the other cases the symptoms, physical findings, course, and results of occasional examinations of the blood, urine, etc., were recorded.

### ONSET

Good histories of many patients were obtained, especially of nurses taken ill while on duty. Except for minor variations, the onset of the disease was much the same, the attack usually starting suddenly with headache in the frontal region; the others described it as diffuse. Another constant symptom at the onset was pain or ache in the lumbar region, more marked in the female patients. In addition there were vague pains in the limbs, and often in the chest. Fever was constant, usually ranging between 103 and 104 F., although there were a few cases in which the temperature ran as high as 106 F. at the beginning. Thirty-five of 230 patients gave a history of a chill at the onset; in some there was only a "shivery sensation." A few patients complained of sore throat as one of the first manifestations. Several spoke of pains in the right lower quadrant of the abdomen. In a number of women menstruation came on too early, occurring on the first day of the disease.

The symptoms mentioned usually lasted from several hours to a day or so, when a cough would appear, dry and painful at first. A few

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patients also complained of nausea at this time. In the majority no nasal symptoms were present, although sneezing was noted in several; in a few there was a slight discharge from the nose, and epistaxis occurred in a small number. In almost all, the edges and tip of the tongue were markedly red, the rest heavily coated. Most of the patients complained of soreness of the trachea, pointing out that the pain was not in the throat but lower down.

#### COURSE

From the third day the cases may be divided into two groups—mild and severe. As a rule the mild cases were uncomplicated, the severe complicated usually by bronchopneumonia, less often by

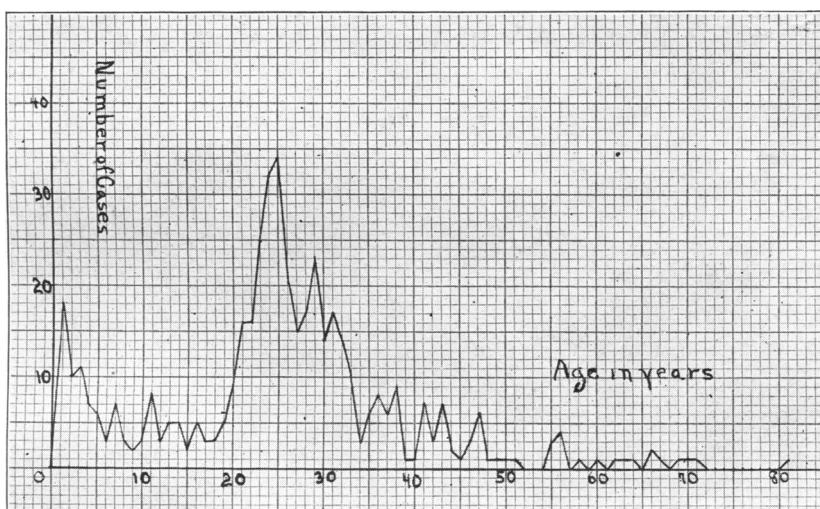


Chart 1.—Distribution according to ages of 546 influenza patients.

empyema or otitis media. In the mild cases the symptoms subsided gradually, the headache being less severe on the 3rd day, the temperature reaching normal on the 5th or 6th day, if not earlier. Many patients, however, complained of dizziness and general weakness for several days and even weeks afterward.

In the severe cases the temperature on the 3rd day would be 102 or 103 F.; or if it had dropped on the 3rd day, which happened in a few cases, it would rise again; the cough, at first dry, would become

productive and painful, and this was usually the signal of a bronchopneumonia, as râles would develop and the general condition would become worse. The cough usually continued until the end of the attack. There were, however, cases in which the cough subsided early. In cases that recovered, the fever usually ended by lysis; in the fatal cases the temperature remained high, sometimes it was 106 or 107, in one case even 109 F. Definite cyanosis was present in eight cases of pneumonia that recovered; in all the fatal cases cyanosis was marked and accompanied with unconsciousness and muscular twitchings. Death usually occurred on the 6th to 11th days of the disease, in a few cases on the 3rd or 4th day.

#### PHYSICAL FINDINGS

In uncomplicated cases there were few physical changes. The tongue was coated, the pharynx slightly congested, and occasionally conjunctivitis was present. The heart, as a rule, showed no change, the pulse, however, was slow in proportion to the temperature. An occasional râle would be heard at times at the base of the lungs; in many cases, however, râles could not be detected.

In the pneumonic form the patient was prostrated, the respiration rapid, although slower than in ordinary pneumonia; the temperature high and the pulse slow; the tongue furred, the edges and tip red; the cough distressing, and often in paroxysms ending in a sort of whoop. In some cases dulness was difficult to detect over the lungs; when present it was not as fixed as in other forms of pneumonia, but often changed from day to day, or even from hour to hour; nearly every case revealed crepitant or subcrepitant râles in some part of the chest; bronchial breathing was less frequent and often heard over small patches only of lung. The most frequent localization of pneumonia was both bases, next the left lower lobe, then the right middle lobe or prevertebral region, the right lower lobe, and least frequently the left and right upper lobes. In the last stages of the disease, however, especially in the fatal cases, moist râles would be heard all over the chest, giving the impression that no spot in the lung was free.

Rigidity of the right rectus abdominalis muscle was found in some patients and not in others. Meningeal symptoms were absent, unless headache and unconsciousness were considered as such.

TABLE 1 \*  
BLOOD COUNTS IN INFLUENZA

Cases	Day of At- tack	Hemo- globin	Red Cor- puscles	Total Num- ber	Leukocytes						Remarks
					Neu- trophils	Small Mono- nu- clears	Large Mono- nu- clears	Transi- tions	Eo- sino- philis	Baso- philis	
1	1	85	6,360,000	6,400	88	8	2	2			
	2	..	.....	4,600	65	24	8	3			
	3	..	.....	3,800	56	43	1				
	4	..	.....	4,600	43	46	11				
	7	..	.....	7,200	44	30	18	4	4		
	9	..	.....	10,200	67	25	7	1			
2	1	..	.....	3,000	76	22	2	..	..	..	In the 6th week after recovery, the leuko- cytes num- bered 11,600
	2	75	.....	6,200	58	42					
	3	65	.....	3,000	54	44	2				
	4	85	.....	5,000	70	26	4				
	5	85	.....	4,600	50	36	12	..	..	2 (?)	
	6	85	3,920,000	3,600	46	40	14				
	11	65	4,560,000	6,600	79	20	10				
3	1	85	5,560,000	6,200	58	31	9	2			
	3	90	.....	5,400	52	42	6				
	4	85	.....	3,600	48	38	10	4			
	6	..	.....	5,000	60	34	4	2			
	9	75	4,960,000	9,800	68	32					
	14	75	6,120,000	5,800	46	40	12	..	2		
4	1	95	5,760,000	4,200	56	54	..	..	..	..	Patient per- fectly well after the ninth day
	2	85	5,400,000	4,400	68	32					
	5	85	5,880,000	6,800	76	24	3				
	6	95	.....	9,000	75	22					
	9	..	.....	14,200							
	23	95	5,080,000	16,400	52	32	16				
5	2	85	5,200,000	6,000	34	62	2	2			
	3	90	5,040,000	5,800	42	54	4	4			
	4	80	5,200,000	4,400	44	52	4				
6	1	90	.....	3,800							
	4	90	4,840,000	4,600	38	59	3				
	8	75	5,040,000	10,200	71	17	10	1	..	..	Well
7	3	90	.....	5,900							
	4	..	.....	5,400							
	5	..	.....	4,600							
	6	..	.....	4,500	76	24					
	7	85	.....	4,400	80	19	1				
	28	95	4,920,000	10,800	60	36	4				
8	1	95	4,250,000	6,000							
	4	95	4,240,000	15,800	88	7	5	..	..	..	Pneumonia developed
	5	90	4,240,000	11,800	68	28	4				
	7	80	3,880,000	7,800	60	36	2	2			
	10	90	4,720,000	7,600	76	20	4				
9	2	..	.....	6,600	86	11	2	..	1 (?)	..	Pneumonia developed
	3	..	.....	10,800	92	8	..	..	..	..	
	4	..	.....	7,000	94	6					
	5	..	.....	9,200	68	32					
	7	75	.....	12,000	84	14	2	2			
	10	65	4,800,000	17,000	74	19	5	2			
	12	..	.....	23,000							
	14	85	3,520,000	9,200	76	14	10				
	17	85	3,600,000	13,600	60	40					
	22	75	3,240,000	15,000	72	24	2	2			
10	1	..	.....	5,200							
	2	95	.....	30,000	90	5	5	..	..	..	Pneumonia developed
	4	85	4,200,000	15,600	83	14	3				
	9	85	.....	15,400	78	10	2				
	14	85	5,640,000	22,800	80	12	5	1	2		
	28	75	4,800,000	12,400							

TABLE 1 (*Continued*)  
BLOOD COUNTS IN INFLUENZA

Cases	Day of Attack	Hemo-globin	Red Cor-puscles	Leukoocytes							Remarks
				Total Number	Neu-tro-phils	Small Mono-nu-clears	Large Mono-nu-clears	Transi-tions	Eo-sino-phils	Baso-phils	
11	1	85	.....	5,200	84	16					Pneumonia developed
	2	85	5,200,000	3,200	50	48	2	..	..	..	
	3	85	4,640,000	6,000	90	18	2				
	7	75	4,200,000	10,200	98	2					
	8	85	5,200,000	16,200							
12	1	..	.....	3,400							Otitis media developed
	2	..	3,120,000	5,400	54	24	8	2			
	3	90	3,640,000	3,400	62	22	14	2			
	5	85	3,880,000	3,200	48	52					
	7	..	.....	10,600	78	18	4	..	..	..	
13											
	1	..	.....	4,000							Pneumonia
	2	95	5,080,000	3,400	52	44	4				
	3	95	.....	3,600	58	36	6				
	4	95	4,040,000	3,200	54	44	2	..	..	..	
	5	80	3,680,000	6,200	46	46	8				
	6	80	4,200,000	4,200	60	34	6				
	8	80	4,720,000	7,000	88	12					
14	1	..	.....	4,900	81	18	1				Pneumonia
	2	..	.....	4,400	66	24					
	3	85	.....	4,800	64	30	4	2			
	4	85	5,600,000	6,000	54	45	1	..	..	..	
	5	85	.....	6,000	64	32	4				
	6	95	5,160,000	5,800	48	48	4				
	10	95	4,400,000	14,000	92	4	4				
15	1	85	.....	5,800	82	18					Pneumonia
	2	90	.....	4,400	66	34					
	3	85	4,120,000	5,800	70	24	4	2			
	5	85	4,320,000	2,800	70	22	8				
	10	80	4,400,000	9,000	76	22	2	..	..	..	
	12	85	6,200,000	18,000	82	16	2				
16	1	85	3,040,000	5,000	22	74	4				Child
	2	85	4,000,000	7,400	36	64					
	4	85	4,040,000	4,800	28	72					
	6	80	4,120,000	8,200	30	64	6				
	8	80	.....	6,400	64	24	10	2			
17	1	95	4,000,000	6,800	27	66	7				Child
	2	95	.....	7,200	48	50	2				
	4	85	5,680,000	7,400	36	62	2				
	6	85	5,160,000	3,600	28	64	6	2			
	8	85	5,200,000	15,200	37	63					
18	1	85	5,600,000	6,900	42	56	2				Child
	2	85	6,160,000	7,200	60	36	4				
	4	85	4,200,000	7,200	56	30	10	2	2		
	10	85	6,300,000	16,100	56	28	9	6	1		
19	1	90	6,100,000	9,000	50	34	10	6			Child
	2	85	4,720,000	4,600	16	80	4				
	4	85	5,640,000	8,400	46	50	4				
	10	95	6,550,000	8,700	40	40	10	8	2		

\* The 19 cases of this table are illustrative of the blood findings in the 55 cases studied.

BLOOD (TABLE I)

Blood counts and blood pressure determination were made about 11 a. m.. Wherever possible, blood was examined some time after

the patient had recovered, for comparison. For the differential counts carbolthionin and Wright stains were used.

Nearly all the uncomplicated cases showed leukopenia and lymphocytosis. At the onset the leukocytes numbered from 4,000 to 6,400 per c.mm. After the 1st day they began to decrease in number, being 2,000 to 3,000 on the 2nd, 3rd and 4th days. The leukopenia persisted until the patient was well on the road to recovery when the count would rise to 9,800-14,000. This leukocytosis usually developed between the 6th and 8th days of the attack.

The differential count was also characteristic. There was a change from the normal differential count (sometimes there was a neutrophilia on the 1st day) to a relative lymphocytosis on the 2nd or 3rd day. The rise in lymphocytes which was gradual reached at times 50-55%. This condition persisted until the patient recovered, when the neutrophils rose to 67 or 70%. This, however, was only temporary, the count on the next day or two often showing again a relative lymphocytosis.

The development of complications sometimes was associated with a change from leukopenia with relative lymphocytosis to leukocytosis with relative neutrophilia (Table 1, Cases 8-12). In other cases, however, complications did not change the blood picture; this was true especially in some cases that developed pneumonia (Table 1, Cases 13-15). Even in those cases in which complication was followed by a leukocytosis the count was not as high as in many pyogenic infections. In fact, some of the cases of pneumonia gave a higher leukocyte count after the pneumonia subsided than during the active stage. In three fatal cases leukocytosis (12,000-16,000) with neutrophilia was found before death, with 86-98% neutrophils.

No basophils, and only a very few eosinophils were found. As a rule, there were no transitional cells in the blood. Occasionally, however, the smears would contain many transitional cells.

In the uncomplicated cases the red cells were not affected, either in number or structure. In cases with pneumonia a low red count might be obtained toward the end. Nucleated red cells were not found. The hemoglobin was not affected in any of the cases.

#### BLOOD PRESSURE

The blood pressure was found to give a fairly uniform curve. Normal at the onset, the pressure, both systolic and diastolic, but especially the latter would gradually fall. For instance, a patient with

a systolic pressure on the 1st day of 130 and a diastolic pressure of 90 would show the following variations from day to day; 2nd day, systolic pressure 120, diastolic 70; 3rd day, systolic 110, diastolic 55; 4th and 5th days, systolic 105 and diastolic 50, the pressure now usually remaining constant for several days after which it would begin to rise again. In one case the diastolic pressure fell as low as 35. The fall in pressure was observed in uncomplicated as well as in complicated cases.

#### URINE

In uncomplicated cases the urine, as a rule, was normal, but occasionally a trace of albumin was noted. In most cases that developed pneumonia the urine showed more or less albumin, and in some there were hyaline and granular casts. In the fatal cases there were practically always many granular and hyaline casts 2 to 3 days before death. In two cases hematuria developed 2 days before death. Acetone was absent in most cases.

#### THE SPUTUM

The sputum was tenacious at the beginning of pneumonia and usually remained so for 3 or 4 days, after which it became frothy. In some cases, however, it remained tenacious for a much longer period. The color of the sputum was yellow at first; later, however, it became rusty and often looked as though it consisted entirely of blood, especially in the fatal cases. Microscopically, the sputum usually showed pneumococci, streptococci and staphylococci. Influenza-like bacilli were seen in only a few cases.

#### COMPLICATIONS

Besides pneumonia, the cases presented comparatively few complications. There were 12 cases of otitis media in the 546 cases of influenza observed, 8 of empyema (hemolytic streptococci in 50%), 1 of lung abscess, 1 of hemoptysis, 3 of myocarditis, 2 of hematuria, 2 of retention of urine, 3 of jaundice, 1 of profuse uterine hemorrhage, 19 of premature menstruation, 1 of cervical cellulitis, 1 of multiple abscess, 2 of maculo-papular rash, 3 with decided muscular twitchings and 2 of delirium. Psychosis developed in 2 cases.

#### PROGNOSIS

Of the 454 adults treated in the hospital, 80 died, approximately 20%, and of the 92 children, 10 died, approximately 11%. The

greatest number died in October, the early part of the epidemic. Of the 80 fatal adult cases, 43 were women and 37 men. As eight of the fatal cases in women were complicated by pregnancy, and as the rate of admission of women compared to men was 2 to 1, it would seem that more men died from influenza than women. The highest mortality in both cases was between the ages of 20 and 30.

In practically all the fatal cases pneumonia was present. Rest in bed from the beginning of the attack seemed to have a favorable effect. Most of the nurses, who went to bed immediately after taking sick, recovered; while of those who remained on duty for 2 or 3 days many died. The fever seemed to have no direct relation to the outcome, some patients with a temperature of 106 F. at the beginning recovered, while others who ran relatively low temperatures died.

Of the 15 pregnant women, 8 died, 5 being in the 7th month and 3 at full term. Five of the 8 that died miscarried before death. Of the 7 that recovered, 3 were at full term, 2 in the 8th month, and 2 in the 7th. Existing heart lesions increased the danger from influenza. Cyanosis is an unfavorable prognostic sign and was present in practically all the fatal cases.

#### INFLUENZA IN CHILDREN

In 92 cases observed, the symptoms of influenza in children differed from those of adults in degree rather than kind. Vomiting was more frequent in children. The temperature was lower than in the adults, particularly in the fatal cases. Sneezing at the onset was more frequent, also coryza and conjunctivitis. Epistaxis was common on the 2nd or 3rd day. In practically every case the throat was congested, and sometimes even fiery red. The cough was more spasmodic than in adults, resembling whooping cough closely. Expectoration was noted in one case only. Cyanosis was observed only in the fatal cases.

The course of the disease in children, like that in adults, was mild or severe, that is, there were two groups of cases, those that did not develop pneumonia and those that did. The physical findings in the former were practically nil, except for a pharyngitis which was aggravated by irritation from the cough. The rash noted in a few cases could be traced to belladonna or serum; it usually occurred late in the attack or after it had subsided. In twelve cases I noticed, opposite the second molar, a group of shining round vesicles closely aggregated, the mucous membrane all around being markedly congested. This condition lasted from 3-4 days.

In the severe or pneumonic form the physical findings varied, the only constant one being subcrepitant râles over the affected area. Bronchial breathing and localized dulness were made out in about half the cases, the dulness frequently traveling from one spot to another, the signs varying at different times of the day. Pneumonia was most frequently localized at the base of the lungs and next at the right middle lobe. Herpes labialis occurred more often in children than in adults.

Allowing for the normal differences in the blood of children and of adults, the changes in the blood in influenza seem to be about the same, namely, leukopenia and lymphocytosis, the leukocyte count running from 6,000-8,400, which of course is a leukopenia for children (Table 1, Cases 16-19). A leukocytosis takes place on recovery. In most uncomplicated cases the differential count showed a distinct lymphocytosis, although in a few it was normal. The red blood cells were usually below five million.

The urine in children as a rule was normal, albumin generally absent.

There were three cases of otitis. Meningitis was not observed, and symptoms of meningeal irritation were infrequent. The result in children was more favorable than in adults — of 92 children, 10 died, approximately 11%.

#### SUMMARY

The greatest number of the cases in this series occurred between the ages of 20 and 30, corresponding to the experience of most observers. In addition there were, current opinion to the contrary notwithstanding, a good many cases in very young children. Headache, pain in the lumbar region, and fever, were constant symptoms at the onset. Most patients also complained of soreness of the trachea. Only a few patients complained of sore throat. Chills, described by some as of frequent occurrence, were noted only occasionally.

In adults, I observed only two maculopapular rashes, both of which resembled drug rashes and occurred after the administration of belladonna and bromids. Meningeal symptoms, reported by some, were absent. The blood, described usually as showing a neutrophilia, in the cases I studied gave a lymphocytosis at certain stages of the disease, with leukocytosis and neutrophilia on recovery. The blood pressure gave a regular downward curve. In 12 children I observed an endanthem in the mouth which may be of significance.

The cases studied do not justify a classification into respiratory, gastro-intestinal and nervous types, as all cases were essentially respiratory. There were fewer nervous manifestations in the influenza with bronchopneumonia than in ordinary pneumonia.

The diagnosis of the disease, I believe, may be made from the sudden onset, headache, backache, pain in the limbs, fever, leukopenia, lymphocytosis, slow pulse and low blood pressure. These symptoms should be sufficient to differentiate influenza from the ordinary respiratory infections with conjunctivitis, sore throat, coryza, and leukocytosis.

From a study of the blood the suggestion arises that two types of pneumonia may complicate influenza; one associated with leukopenia, and hence possibly caused by the same organism that produces the original influenza, and the other with a leukocytosis and due in all probability to secondary infection by better known organisms.